Letter to the Editor
Prostate diseases and male voiding dysfunctions

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Cross Talk between the Ketogenic Diet and Metastatic Prostate Cancer Cells

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The article by Chirumbolo et al [1], provides comprehensive insight into the role of lipid enriched diet in the prevention of cancer by acting as modulatory signalling molecules. The ketogenic diet (KD) is a high fat and low carbohydrate diet that produces ketone bodies by mimicking starvation [2]. Obesity is associated with a significant increased risk of progression to high-grade prostate cancer (PCa) [2]. However, the KD significantly improves weight loss [2], and might mitigate tumour progression in patients with metastatic PCa.

The KD has been revealed to increase the effectiveness of radio/chemotherapy *in vivo* [2]. The KD mitigate oxidative stress and improve the endogenous antioxidant defense system [2]. D-β-hydroxybutyrate (βHB), a ketone body synthesized in the liver through the metabolism of fatty acids, is an endogenous inhibitor of class I histone deacetylases (HDACs) [3]. Class I HDACs inhibitors have been revealed to inhibit PCa proliferation in animal models [3]. βHB supplementation increased histone acetylation in mouse tissues [3]. Inhibition of HDAC by βHB was associated with changes in transcription, in the genes encoding oxidative stress resistance factors (Forkhead box class O 3a and Metallothionein 2) [3]. Moreover, administration of βHB in mice offered significant protection against oxidative stress, *via* upregulation of the antioxidant defense mechanisms [3].

βHB supplementation decreased tumor cell proliferation, viability and prolonged the survival of mice with metastatic cancer, *via* the Warburg effect [4]. The Warburg effect encompasses a vital weakness of cancer cells, pertaining to cancer cells dependence on excess glucose for survival and proliferation, which is prominent in metastatic cells [4]. Interestingly, PCa cells switch to the Warburg effect only in the metastatic stage [5], and ketone bodies inhibit glycolysis, consequently reducing the main pathway of energy production for metastatic cancer cells [4]. Moreover, cancer cells do not utilize ketones effectively for energy production, because of mitochondrial dysfunction [4].

In conclusion, metastatic PCa cells may not efficiently utilize ketone bodies for energy production. Moreover, the KG may slow down the proliferation of PCa cells, and consequently prevent metastasis. However, further preclinical, and clinical studies are needed to substantiate the effects of ketone bodies on the proliferation of metastatic PCa cells.

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Conflict of Interest

The authors have nothing to disclose.

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